aetna®

Benign Prostatic Hypertrophy (BPH) Treatments

Number: 0079

Policy

Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers the following approaches to the treatment of benign prostatic hypertrophy (BPH) medically necessary for members with benign prostatic hypertrophy as alternatives to transurethral resection of the prostate (TURP):

  A. Alpha adrenergic blockers (alfuzosin, doxazosin, silodosin, tamsulosin, and terazosin)

  B. Hormonal manipulation (including finasteride, dutasteride, and dutasteride plus tamsulosin)

  C. Interstitial laser coagulation of the prostate (ILCP)

  D. Laser prostatectomy

  E. Laser based procedures including contact laser ablation of the prostate (CLAP), holmium laser procedures of the prostate (HoLAP, HoLEP, HoLRP), photoselective laser vaporization of the prostate (PVP), transurethral ultrasound-guided laser induced prostatectomy (TULIP), and visually-guided laser ablation of the prostate (VLAP,

Policy History

Last Review   12/31/2016

Effective: 11/17/1995

Next Review: 01/26/2017

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

also called non-contact laser ablation of the prostate)z

F. Prostatic urethral lift (e.g., the UroLift)

G. Tadalafil (5 mg daily dose) (Note: Some plans exclude coverage of tadalafil; please check benefit plan descriptions)

H. Transurethral electrovaporization of the prostate (TUVP)

I. Transurethral incision of the prostate (TUIP)

J. Transurethral microwave thermotherapy (TUMT)

K. Transurethral needle ablation (TUNA), also known as transurethral radiofrequency needle ablation (RFNA) (including TUNA using water vapor, Rezum system)

L. Ultrasonic aspiration.

Laser prostatecctomy, ILCP, other laser based prostate procedures, prostatic urethral lift, TUVP, TUIP, TUMT, TUNA and ultrasonic aspiration of prostate are experimental and investigational for other indications. See also **CPB 0100 - Cryoablation (../100_199/0100.html)**.

II. Aetna considers the UroLume endourethral prosthesis (urethral stent) medically necessary to relieve prostatic obstruction secondary to BPH in men at least 60 years of age, or men under 60 years of age who are poor surgical candidates, and whose prostates are at least 2.5 cm in length. (Note: UroLume is not intended for temporary use). UroLume endourethral prosthesis is also considered medically necessary for the treatment of recurrent bulbar urethral stenoses/strictures when previous therapeutic approaches such as dilation, urethrotomy or urethroplasty have failed (i.e., treatment was ineffective or there is recurrent stricture requiring additional treatment).

Aetna considers the UroLume endourethral prosthesis experimental and investigational for other indications because its effectiveness for indications other than the ones listed above has not been established.

III. Aetna considers the following approaches for the treatment of BPH to be experimental and investigational because the effectiveness of these interventions has not been

established by the peer-reviewed medical literature:

    A. Absolute ethanol injection (transurethral)

    B. Aquablation (water jet-hydrodissection)

    C. Bipolar plasma enucleation

    D. Botulinum toxin

    E. Cryosurgical ablation

    F. Endoscopic balloon dilation of the prostate

    G. Histotripsy

    H. Intra-prostatic injections of vitamin D3 receptor analogs

    I. Lutenizing hormone-releasing hormone antagonists

    J. Mirabegron (Myrbetriq)

    K. Phytotherapy

    L. Plasma kinetic vaporization (PlasmaKinetic Tissue Management System, Gyrus, Maple Grove, MN)

    M. Prostatic arterial embolization (transcatheter embolization)

    N. Temporary prostatic urethral stent

    O. Transrectal thermal therapy (including the Rezum system, transrectal microwave hyperthermia, transrectal radiofrequency hyperthermia, transrectal electrothermal hyperthermia, and transrectal high-intensity focused ultrasound)

    P. Water-induced thermotherapy (also known as hot-water balloon thermoablation and thermourethral hot-water therapy).

Background

This policy is based primarily on the practice guideline of management of benign prostatic hyperplasia (BPH) from the American Urological Association. While a number of treatment modalities have been shown to be effective for BPH, it is not yet evident which of these techniques will prove to be superior or which will approach the effectiveness of transurethral resection of the prostate (TURP) in treating BPH.

Temporary stents are designed primarily for short-term use in the treatment of symptomatic BPH, for a duration of 6 months to 3 years (van Dijk and de la Rosette, 2003). Temporary stents

are made of non-absorbable material, which prevents epithelial ingrowth and therefore allows easy removal. However, this may lead to unintended migration. Some temporary stents are biodegradable, so that they break down into small fragments, which are excreted through the urethra over time. Although no explantation of biodegradable stents is required, the excreted fragments may cause urethral obstruction.

According to the guidelines by the American Urological Association (AUA, 2003), "because prostatic stents are associated with significant complications, such as encrustation, infection and chronic pain, their placement should be considered only in high-risk patients, especially those with urinary retention". AUA guidelines explain: "Clinical trials of temporary prostatic stents are ongoing, and some long-term efficacy and safety studies have been published. It is unclear whether prostatic stents have applications in men with symptomatic BPH who have not developed urinary retention and whose medical conditions permit other forms of treatment."

One temporary prostatic urethral stent currently in development is the Spanner, which is designed for temporary use (30 days or less) in men with bladder outlet obstruction to reduce elevated post-void residual and improve voiding symptoms. The stent design is very similar to the proximal 4 to 6 cm portion of a Foley catheter. It includes a proximal balloon to prevent distal displacement, a urine port situated cephalad to the balloon, and a reinforced stent of various lengths to span most of the prostatic urethra. There is also a distal anchor mechanism attached by sutures, and a retrieval suture which extends to the meatus and deflates the proximal balloon when pulled.

Corica et al (2004) reported that the Spanner significantly improved voiding function and quality of life among patients with prostatic urethral obstruction (n = 30). However, in a review on recent developments in the management of symptomatic BPH, Ogiste and colleagues (2003) stated that the

role of stents as an intermediary in cases of treatment failure, or as definitive therapy for BPH and its associated problems are still unclear, when compared with newer, minimally invasive options. Current literature on stents is relatively sparse. However, recent studies showed that permanent and temporary prostatic urethral stenting are effective in relieving obstruction and urinary retention. Nevertheless larger controlled clinical studies are needed to demonstrate the real value of this intervention.

Azuyma and Chancellor (2004) commented that although the results of the use of bioabsorbable spiral stents are encouraging, "there are still too many failures." The authors state that controlled studies are needed to compare bioabsorbable stents with other forms of therapy.

The California Technology Assessment Forum (2002) concluded that water-induced thermotherapy for BPH does not meet CTAF's technology assessment criteria. The assessment concluded that "[e]xisting studies have not yet demonstrated that WIT results in better health outcomes as much as or more than the established alternative of TURP, TUNA, or microwave thermotherapy." Furthermore, in a review on minimally invasive therapies for BPH, Naspro et al (2005) noted that "currently, transurethral microwave thermotherapy seems to offer the soundest basis for management of the condition, providing the longest term follow up and the largest numbers of studies completed to date. Among surgical alternatives, holmium laser enucleation has gained ground as an encouraging new approach, being similar to standard transurethral resection of the prostate, but reducing perioperative morbidity with the same long-term results. More randomized comparisons correctly conducted need to be undertaken before an accurate general picture is available for the urologist".

Transurethral electrovaporization of the prostate (TUVP) is another alternative, minimally invasive procedures to treat BPH. This procedure combines electrosurgical vaporization and

desiccation to remove obstructive hyperplastic prostatic tissue with minimal morbidity. It entails a special electrosurgical modification involving a grooved roller electrode with a large surface area and multiple edges of contact; thus allowing high current density to be delivered to an extensive area of tissue to be vaporized. The device fits standard resectoscopic equipment, and its use requires no special skills other than those needed for conventional TURP.

Fowler et al (2005) compared the clinical and cost-effectiveness of TUVP with TURP. Men requiring surgery for lower urinary tract symptoms deemed to be due to BPH were recruited from 4 centers in south-east England. Main outcome measures were the International Prostate Symptom Score (IPSS) and the IPSS quality of life (QOL) question. Secondary outcome measures included urinary flow rate, post-void urinary volume, prostate volume and pressure-flow urodynamics. TURP and TUVP were both effective in producing a clinically important reduction in IPSS and positive change in the IPSS QOL question. The success rate for relief of symptoms was 85 % for TURP and 74 % for TUVP. Neither the success of the treatment nor the change in aggregated IPSS was significantly different between the groups. The improvement was sustained to 24 months after treatment with no significant difference between the groups. The effectiveness of both treatments was also equivalent when assessed through improvement in objective measures of urinary tract function, reduction in prostate size and the change in health questions of SF-36. The absolute incidence of adverse events was similar between the 2 groups. The incidence of severe or prolonged bleeding was less with TUVP, as evidenced by the need for blood transfusion and the drop in hemoglobin level 24 hours post-operatively. This study did not show any significant difference in inpatient stay or use of outpatient resources between the groups. The authors concluded that TURP and TUVP are equivalently effective in improving the symptoms of benign prostatic enlargement over at least 2 years. TUVP is associated with less morbidity due to hemorrhage than TURP. This finding is in agreement with that of the National Institute for Health and Clinical Excellence

(2003), which stated that there is adequate support for the use of TUVP, and that of Nohuglu et al (2005) who found that TUVP is as effective as TURP with similar morbidity. The advantages of TUVP are that the urethral catheter is withdrawn earlier, hospitalization is shorter, and bleeding is less.

Thomas et al (2006) noted that botulinum neurotoxin (BoNT) application recently has been extended to prostate disorders. While BoNT has shown promising preliminary results for male lower urinary tract symptoms, and translational research suggests novel mechanism of action of BoNT in the prostate, it is important to remember that the application of BoNT in the prostate is not approved by the regulatory agencies and caution should be applied until larger randomized clinical trials are completed. This is in agreement with the observations of Azzouzi et al (2006) as well as Chuang and Chancellor (2006).

Kuo and Liu (2009) evaluated the effectiveness of BoNT-A in patients with large BPH with an unsatisfactory response to combined alpha-blocker and 5-alpha-reductase inhibitor therapy. A total of 60 patients with total prostate volume (TPV) of greater than 60 ml with unsatisfactory response to combination medical therapy were randomly assigned to receive add-on intra-prostatic BoNT-A injection (n = 30) or continued medical therapy (control group). Patients in the treatment group received 200 to 600 U of Botox injected into the prostate. Outcome parameters including IPSS, quality of life index (QOL-I), TPV, maximum flow rate (Q(max)) and post-void residual (PVR) volume were compared between treatment and control groups at baseline, 6 months and 12 months. Significant decreases in IPSS, QOL-I and TPV, and increase in Q(max) were observed at 6 months and remained stable at 12 months in the treatment group. Improvements in IPSS and QOL-I were also observed at 6 months and a decrease in TPV at 12 months was noted in the control group. However, no significant changes in any parameters except for QOL-I at 6 and 12 months were noted between the treatment and control groups. Acute urinary retention developed in 3 patients receiving BoNT-A treatment. Three BoNT-A and 2 medical

treatment patients converted to trans-urethral surgery at the end of study. The authors concluded that the findings of this study showed that add-on prostatic BoNT-A medical treatment can reduce prostate volume and improve lower urinary tract symptom score and QOL-I within 6 months in the treatment of large BPH. However, the therapeutic effect at 12 months was similar to combination medical treatment.

Oeconomou and Madersbacher (2010) summarized the mechanisms through which BoNT-A could inhibit the progression of BPH and eliminate the lower urinary tract symptoms (LUTS) according to the findings of animal studies. Furthermore, these researchers reviewed clinical studies to report the safety and effectiveness of intra-prostatic BoNT-A injection according to various injection protocols. The experimental studies reported induced relaxation of the prostate, atrophy, and reduction in its size through inhibition of the trophic effect of the autonomic system on the prostate gland. Also, a possible mechanism of reduction in LUTS might take place through inhibition of sensory afferents from the prostate to the spinal cord. Clinical studies reported symptomatic relief and improvement in the measured parameters during the follow-up period, whereas local or systematic side-effects are rare. The authors concluded that it should be recognized that, at present, this therapy is still experimental. Although the results of the clinical studies are encouraging, the level of evidence is low. Large-scale, clinical, placebo-controlled, randomized studies, including long-term surveillance to document the evidence of this therapy are needed.

In a phase II prospective study, Richter et al (2009) recorded the effectiveness and complications of holmium laser enucleation of the prostate (HoLEP) in the first post-operative year. Eighty-six of 343 consecutive patients with benign prostatic obstruction (IPSS greater than 10] were treated with the VersaPulse 100-W laser (Lumenis), 2.0 J/50 Hz or 3.2 J/25 Hz. Pre-operative and post-operative prostate-specific antigen (PSA), Q(max), IPSS, prostate gland volume, and PVR volume

were prospectively measured. The median follow-up time was 8 months (3 to 21). Median patient age was 71 (50 to 83) years, and mean operating time was 77.5 (9 to 135) mins. There was only 1 case of significant bleeding. In 14 of 86 cases (16 %), HoLEP was combined with TURP. Short-term voiding complaints were expressed by 26.7 % of the questioned patients. The length of hospital stay was in most cases less than 48 hrs. IPSS, Q(max), PSA, PVR volume, gland volumes, and QOL improved significantly after 3 months, and all parameters remained unchanged after 12 months. The re-operation rate within 12 months was 6.8 %. The authors concluded that the advantage of HoLEP over TURP is the very low bleeding rate and thus a shorter hospital stay and possible out-patient therapy. In particular, patients with prostate gland volume less than 50 mls profit from HoLEP. Post-operative voiding complaints are comparable to those with TURP. Moreover, the authors stated that long-term results are needed to confirm the low re-operation rate.

Erol et al (2009) prospectively evaluated vaporization efficiency of the high-power, 980-nm diode laser for bladder outlet obstruction due to BPH. A total of 47 consecutive patients were included in the study. Inclusion criteria were maximal flow rate 12 ml per second or less with voided volume 150 ml or greater, IPSS of 12 or greater, and QOL score 3 or greater. Patients with a history of neurogenic voiding dysfunction, chronic prostatitis, or prostate or bladder cancer were excluded from analysis. Pre-operative maximal flow rate, post-void residual urine, IPSS, QOL, International Index of Erectile Function-5, PSA, and prostate volume were compared with values at 3 and 6 months. Complications were assessed. Month 3 assessment revealed that the mean (+/- SD) IPSS decreased significantly from 21.93 +/- 4.88 to 10.31 +/- 3.79 (p = 0.0001). The mean maximal flow rate increased significantly from 8.87 +/- 2.18 to 17.51 +/- 4.09 ml per second (p = 0.0001). Quality of life score changed considerably compared to baseline. All of these values showed slight improvement at month 6. There was no deterioration in erectile function according to the International Index of Erectile Function-5 short

form. Post-void residual urine decreased significantly; reductions in prostate volume and PSA were also significant. The most common post-operative complications were retrograde ejaculation (13 of 41 patients or 31.7 %) and irritative symptoms (11 of 47 or 23.4 %), which subsided in the maximal flow rate at 2 weeks. Re-catheterization was necessary in 2 patients due to urinary retention after catheter removal; 2 patients had temporary combined urge and stress incontinence for 2 weeks. Late bleeding in 1 patient 4 weeks post-operatively resulted in catheterization and irrigation. The authors concluded that the high-power diode laser provided significant improvements in IPSS and the maximal flow rate with low morbidity. Thus, these results of prostate vaporization with the high-power diode laser, representing what is to the authors' knowledge the first clinical study in the literature, are encouraging. The authors stated that further randomized clinical trials are needed to ascertain the role of high-power diode laser as an alternative to TURP or other laser techniques for BPH.

Van Cleynenbreugel et al (2009) presented recent clinical and urodynamic data on trans-urethral photo-selective vaporization of the prostate, and reported on the recent introduction of the 120-W GreenLight laser (GLL) high-performance system. These researchers noted that recent studies confirm improved urodynamic findings following GLL treatment. Moreover, it can be used safely in high-risk patients (e.g., those on anti-coagulant medication and patients with cardiopulmonary diseases), and has been proposed as an alternative to prostate enucleation for larger glands. The introduction of the 120-W high-performance system GLL does, however, place distinct demands on training and operative schemes. The authors concluded that the clinical results of GreenLight prostate vaporization are equivalent to those following TURP, with reduced operative risks, even for the high-risk patient. These clinical benefits have been confirmed by improved urodynamic parameters. Moreover, they noted that the potential advantages of the new 120-W high-performance system GLL have yet to be validated in larger randomized trials.

Ruszat et al (2008) evaluated the intermediate-term clinical effectiveness and the rate of complications in 80-W photo-selective vaporization of the prostate (PVP) with the potassium-titanyl-phosphate laser (GreenLight, Minnetonka, MN) compared with TURP in a prospective non-randomized 2-center study. A total of 396 patients (PVP = 269, TURP = 127) with lower urinary tract symptoms secondary to BPH were included in the study. There was a significant difference in mean age (72 years for PVP versus 68 for TURP, p = 0.001). Patients were therefore stratified in age categories (less than 70, 70 to 80, greater than 80 years) and compared for peri-operative variables, functional outcome and complications, with a follow-up of up to 24 months. The mean prostate size was greater (overall, 62 versus 48 mls, p < 0.001) and mean operative duration longer (overall 72 versus 53 mins; p = 0.001) for PVP in all age categories. The rate of intra-operative bleeding (3 % versus 11 %), blood transfusions (0 % versus 5.5 %) and capsule perforations (0.4 % versus 6.3 %), and early post-operative clot retention (0.4 % versus 3.9 %) was significantly lower for PVP. Hospitalization time was significantly shorter in the PVP group for patients aged less than 70 years (3.0 versus 4.7 days) and 70 to 80 years (4.0 versus 5.0 days; p = 0.001). The improvement of peak urinary flow rate was higher after TURP for any age category. The IPSS and PVR volume during the follow-up showed no significant difference. After 12 months, the overall prostate size reduction was 63 % (-30 mls) after TURP and 44 % (-27 mls) after PVP. The rate of repeat TURP/PVP was higher in the PVP group (6.7 % versus 3.9 %, not significant) within the follow-up of up to 2 years. The incidence of urethral and bladder neck strictures was comparable. The authors concluded that PVP was more favorable in terms of peri-operative safety. Although patients assigned for PVP were older and had larger prostates, PVP resulted in a similar functional outcome. They stated that further follow-up is needed to draw final conclusions about the long-term effectiveness of PVP.

Naspro and colleagues (2009) noted that HoLEP and 532-nm laser vaporization of the prostate (with potassium titanyl

phosphate [KTP] or lithium borate [LBO]) are promising alternatives to TURP and open prostatectomy (OP). These investigators evaluated the safety, effectiveness, and durability by analyzing the most recent evidence of both techniques, aiming to identify advantages, pitfalls, and unresolved issues. A Medline search of recently published data (2006 to 2008) regarding both techniques over the last 2 years (January 2006 to September 2008) was performed using evidence obtained from randomized trials (level of evidence: 1b), well-designed controlled studies without randomization (level of evidence: 2a), individual cohort studies (level of evidence: 2b), individual case control studies (level of evidence: 3), and case series (level of evidence: 4). In the last 2 years, several case-control and cohort studies have demonstrated reproducibility, safety, and effectiveness of HoLEP and 80-W KTP laser vaporization. Four randomized controlled trials (RCTs) were available for HoLEP, 2 compared with TURP and 2 compared with OP, with follow-up greater than 24 months. Results confirmed general effectiveness and durability of HoLEP, as compared with both standard techniques. Only 2 RCTs were available comparing KTP laser vaporization with TURP with short-term follow-up, and only 1 RCT was available comparing KTP laser vaporization with OP. The results confirmed the overall low peri-operative morbidity of KTP laser vaporization, although effectiveness was comparable to TURP in the short-term, despite a higher re-operation rate. The authors concluded that although they are at different points of maturation, KTP or LBO laser vaporization and HoLEP are promising alternatives to both TURP and OP; KTP laser vaporization needs further evaluation to define the re-operation rate. Increasing the number of quality prospective RCTs with adequate follow-up is mandatory to tailor each technique to the right patient.

Chung and Te (2009) stated that traditionally, the gold standard for treatment of BPH has been the electrocautery-based TURP. However, the number of laser techniques being performed is rapidly increasing. Potential advantages of laser therapy over traditional TURP include decreased morbidity and shorter hospital stay. There are several techniques for laser

prostatectomy that continue to evolve. The main competing techniques are currently the HoLEP and the 80-W 532-nm laser prostatectomy. The HoLEP, using the Holmium:YAG laser, has been shown to have clinical results similar to TURP and is suitable for patients on anti-coagulation as well as those with large prostates. Disadvantages of this technique are the high learning curve and requirement of a morcellator. When used to treat BPH, studies have demonstrated that, like the HoLEP, the 80-W KTP laser is safe and effective in patients with large prostates and in those taking oral anti-coagulation. Several studies have compared these 2 techniques to TURP. Frequently reported advantages of the HoLEP over the 80-W laser prostatectomy are the availability after the procedure of a pathology specimen and ability to remove a higher percentage of prostate tissue during resection. However, the trans-urethral laser enucleation of the prostate addresses these concerns and has shown to have durable outcomes at 2-year follow-up. Two new laser systems and techniques, the thulium laser and the 980-nm laser, have emerged recently. However, clinical data from these procedures are in their infancy and large long-term studies are needed to ascertain their clinical effectiveness.

Lourenco and colleagues (2008) ascertained the clinical effectiveness and cost utility of procedures alternative to TURP for BPH unresponsive to expectant, non-surgical treatments. Electronic searches of 13 databases to identify relevant RCTs were carried out. Two reviewers independently assessed study quality and extracted data. The International Prostate Symptom Score/American Urological Association (IPSS/AUA) symptom score was the primary outcome; others included QOL, peak urine flow rate and adverse effects. Cost-effectiveness was assessed using a Markov model reflecting likely care pathways. A total of 156 reports describing 88 RCTs were included. Most had fewer than 100 participants (range of 12 to 234). It was found that TURP provided consistent, high-level, long-term symptomatic improvement. Minimally invasive procedures resulted in less marked improvement. Ablative procedures gave improvements equivalent to TURP. Furthermore, HoLEP resulted in greater improvement in flow

rate. Holmium laser enucleation of the prostate is unique amongst the newer technologies in offering an advantage in urodynamic outcomes over TURP, although long-term follow-up data are lacking. Severe blood loss was more common following TURP. Rates of incontinence were similar across all interventions other than TUNA and laser coagulation, for which lower rates were reported. Acute retention and re-operation were commoner with newer technologies, especially minimally invasive interventions. The economic model suggested that minimally invasive procedures were unlikely to be cost-effective compared with TURP. Transurethral vaporization of the prostate was both less costly and less effective than TURP; whereas HoLEP was estimated to be more cost-effective than a single TURP but less effective than a strategy involving repeat TURP, if necessary. The base-case analysis suggested an 80 % chance that TUVP, followed by HoLEP if required, would be cost-effective at a threshold of 20,000 pounds per quality-adjusted life-year. At a 50,000 pounds threshold, TUVP, followed by TURP as required, would be cost-effective, although considerable uncertainty surrounds this finding. The main limitations are the quantity and quality of the data available, in the context of multiple comparisons.   The authors concluded that in the absence of strong evidence in favor of newer methods, the standard -- TURP -- remains both clinically effective and cost-effective. There is a need for further research to establish (i) how many years of medical treatment are necessary to offset the cost of treatment with a minimally invasive or ablative intervention; (ii) more cost-effective alternatives to TURP; and (iii) strategies to improve outcomes after TURP.

Hashim and Abrams (2010) noted that benign prostatic enlargement (BPE) leading to benign prostatic obstruction (BPO) affects an increasing number of men as they grow older. They can affect QOL and cause LUTS including urinary retention. The currently available pharmacotherapies are alpha-blockers and 5-alpha reductase inhibitors, which may be effective but can have adverse effects and long-term compliance problems. Thus, it is important to find new medical

treatments for LUTS/BPO and this review aimed to identify the potential future drugs undergoing clinical trials in this field. Articles were identified by means of a computerized Google, PubMed and Cochrane Library search over the last 10 years (using the following keywords: benign prostate hyperplasia, enlargement and obstruction) and a search of the PharmaProjects database. The exact etiology of BPH and its consequences, BPE and BPO, are not known; however, aging and functioning testes have been implicated. Several classes of drugs are currently undergoing clinical trials such as phosphodiesterase-5 (PDE5) inhibitors and lutenizing hormone-releasing hormone antagonists. Others include phytoestrogens, progestogens, NX1207 and PRX302. Some of these work by affecting testosterone level and, therefore, on the static component of BPO, while it is not known how the rest work. The authors stated that until the exact etiology of BPH/BPE/BPO is known, it is unlikely the cure for this disorder will be found.

Wang (2010) examined the use of PDE5 inhibitors for BPH/LUTS treatment and highlighted the clinical significance. Pre-clinical and clinical studies have provided promising evidence that PDE5 inhibitors may be an effective and well-tolerated treatment option for BPH/LUTS. Combination therapy using PDE5 inhibitors and alpha1-adrenergic blockers resulted in greater improvements in BPH/LUTS than did either drug alone. There has been increasing interest in the use of PDE5 inhibitors to treat BPH/LUTS. Combination of PDE5 inhibitors and alpha1-adrenergic blockers may have an additive beneficial effect on BPH/LUTS compared with monotherapy. Mechanisms of action of nitric oxide/cyclic guanosine monophosphate/PDE5 pathway in the treatment of BPH/LUTS deserve further investigations. The author concluded that larger-scale, well-designed clinical trials are needed to ascertain the safety, effectiveness and cost-effectiveness of PDE5 inhibitors in the treatment of LUTS secondary to BPH.

Andersson et al (2011) reviewed the published literature describing the pathophysiology of male LUTS, with an emphasis

on mechanisms that may be modulated or improved by PDE5 inhibition. Literature (through March 2010) was obtained via Medline searches and from the individual reviewers files. Articles were selected for review based on describing in-vitro, pre-clinical, or clinical studies of pathological processes contributing to LUTS, or possible effects of PDE5 inhibition in the lower urinary tract. Major mechanisms contributing to LUTS include: reduced nitric oxide/cyclic guanosine monophosphate signaling; increased RhoA kinase pathway activity; autonomic over-activity; increased bladder afferent activity; and pelvic ischemia. Tadalafil and other PDE5 inhibitors have demonstrated beneficial effects on smooth muscle relaxation, smooth muscle and endothelial cell proliferation, nerve activity, and tissue perfusion that may impact LUTS in men. The authors concluded that the pathophysiology of male LUTS is complex and not completely understood. LUTS may occur independently of BPH or secondary to BPH but in both cases involve obstructive or irritative mechanisms with substantial pathophysiological overlap. While the precise mechanism remains unclear, inhibition of PDE5 seems to have an effect on several pathways that may impact LUTS.

On October 6, 2011, the FDA approved tadalafil (Cialis) for the treatmentof of BPH, and for the treatment of BPH and erectile dysfunction (ED), when the conditions occur simultaneously. Tadalafil should not be used in patients taking nitrates (e.g., nitroglycerin) because the combination can cause an unsafe decrease in blood pressure.   Also, the use of tadalafil in combination with alpha blockers for the treatment of BPH is not recommended because the combination has not been adequately studied for the treatment of BPH, and there is a risk of lowering blood pressure. In 2 clinical trials, men with BPH who took 5 mg of tadalafil once-daily experienced a statistically significant improvement in their symptoms of BPH compared to men who were treated with placebo. The trials based their findings on a reduction in total IPSS scores. In a 3rd study, men who experienced both erectile dysfunction (ED) and BPH and who took 5 mg of tadalafil once-daily had improvement in both

their symptoms of BPH and in their ED compared to men who were treated with placebo. The improvement in ED was measured using the Erectile Function domain score of the International Index of Erectile Function.

While surgical resection and ablation using many different forms of energy remain the reference standard for BPH treatment, many patients seek a less invasive approach that will improve symptoms but not risk the complications associated with tissue removal. The UroLift system (NeoTract Inc., Pleasanton, CA) permanent implant is such a modality; it is delivered under cystoscopic visualization. The implant "holds open" the lateral prostatic lobes creating a passage through the obstructed prostatic urethra. Voiding and symptoms are significantly improved without the morbidity or possible complications following prostate resection. The entire procedure can be readily performed using local anesthesia (Barkin et al, 2012).

On September 13, 2013, the FDA approved the marketing of the UroLift, the first permanent implant to relieve low or blocked urine flow in men aged 50 and older with BPH. Minor adverse events reported included pain or burning during urination, blood in the urine, frequent or urgent need to urinate, incomplete emptying of the bladder, and decreased urine flow.

Chin et al (2012) evaluated the effectiveness of the prostatic urethral lift in relieving LUTS secondary to BPH. A total of 64 men, aged greater than or equal to 55 years, with moderate-to-severe symptomatic BPH were treated and followed-up at 6 Australian institutions. The treatment consisted of transurethral delivery of small implants to secure the prostatic lobes in an open condition, thereby reducing obstruction of the urethral lumen. The effectiveness, including International Prostate Symptom Score, quality of life, benign prostatic hyperplasia Impact Index, and peak urethral flow rate were assessed at 2 weeks and 3, 6, 12, and 24 months. The effect of this treatment on erectile and ejaculatory function was

assessed using the Sexual Health Inventory for Men and Male Sexual Health Questionnaire for Ejaculatory Dysfunction. The prostatic urethral lift improved LUTS symptoms rapidly and durably. The International Prostate Symptom Score was reduced 42 % at 2 weeks, 49 % at 6 months, and 42 % at 2 years in evaluable patients. The peak flow rate improved by greater than or equal to 30 % (2.4 ml/s) at all intervals compared with baseline. No compromise in sexual function was observed after this treatment. The authors concluded that the findings of the present study demonstrated that LUTS and flow improvements without compromising sexual function. Moreover, they stated that although this was an early study with a small cohort, this therapy showed promise as a new option for patients with LUTS.

Roehrborn et al (2013) reported the first multi-center randomized blinded trial of the prostatic urethral lift for the treatment of LUTS secondary to BPH. Men at least 50 years old with AUASI (American Urological Association Symptom Index) 13 or greater, a maximum flow rate 12 ml/s or less and a prostate 30 to 80 cc were randomized 2:1 between prostatic urethral lift and sham. In the prostatic urethral lift group, small permanent implants are placed within the prostate to retract encroaching lobes and open the prostatic urethra. Sham entailed rigid cystoscopy with sounds mimicking the prostatic urethral lift. The primary end-point was comparison of AUASI reduction at 3 months. The prostatic urethral lift arm subjects were followed to 1 year and assessed for LUTS, peak urinary flow rate, quality of life and sexual function. A total of 206 men were randomized (prostatic urethral lift 140 versus sham 66). The prostatic urethral lift and sham AUASI was reduced by 11.1 ± 7.67 and 5.9 ± 7.66, respectively (p = 0.003), thus meeting the primary end-point. Prostatic urethral lift subjects experienced AUASI reduction from 22.1 baseline to 18.0, 11.0 and 11.1 at 2 weeks, 3 months and 12 months, respectively, p < 0.001. Peak urinary flow rate increased 4.4 ml/s at 3 months and was sustained at 4.0 ml/s at 12 months, p < 0.001. Adverse events were typically mild and transient. There was no occurrence of de-novo ejaculatory or erectile dysfunction. The authors

concluded that the prostatic urethral lift, inserted with the patient under local anesthesia, provided rapid and sustained improvement in symptoms and flow, while preserving sexual function.

McNicholas et al (2013) described the surgical technique and results of a novel minimally invasive implant procedure that offers symptom relief and improved voiding flow in an international series of patients. A total of 102 men with symptomatic BPH were consecutively treated at 7 centers across 5 countries. Patients were evaluated up to a median follow-up of 1 year post-procedure. Average age, prostate size, and IPSS were 68 years, 48 cm(3), and 23, respectively. The prostatic urethral lift mechanically opens the prostatic urethra with UroLift implants that were placed transurethrally under cystoscopic visualization, thereby separating the encroaching prostatic lobes. Patients were evaluated pre- and post-operatively by the IPSS, QOL scale, Benign Prostatic Hyperplasia Impact Index, maximum flow rate (Qmax), and adverse event reports including sexual function. All procedures were completed successfully with a mean of 4.5 implants without serious adverse effects. Patients experienced symptom relief by 2 weeks that was sustained to 12 months. Mean IPSS, QOL, and Qmax improved 36 %, 39 %, and 38 % by 2 weeks, and 52 %, 53 %, and 51 % at 12 months (p < 0.001), respectively. Adverse events were mild and transient. There were no reports of loss of antegrade ejaculation. A total of 6.5% of patients progressed to TURP without complication. The authors concluded that prostatic urethral lift has promise for BPH. It is minimally invasive, can be done under local anesthesia, does not appear to cause retrograde ejaculation, and improves symptoms and voiding flow.

McVary et al (2014) analyzed data obtained from a randomized controlled blinded study of the prostatic urethral lift (PUL) to evaluate the sexual side effects of this novel treatment. Men greater than or equal to 50 years with prostates 30 to 80 cc, IPSS greater than 12, and Qmax less than or equal to 12 ml/s were randomized 2:1 between PUL and sham. Sexual activity

was not an inclusion criterion. In PUL, permanent trans-prostatic implants were placed to retract encroaching lateral lobes and open the prostatic fossa. Sham entailed rigid cystoscopy with sounds to mimic PUL and a blinding screen. Blinded groups were compared at 3 months and active-arm then followed to 12 months for LUTS with IPSS and for sexual function with sexual health inventory for men (SHIM) and Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EjD). Subjects were censored from primary sexual function analysis if they had baseline SHIM less than 5 at enrollment. Secondary stratified analysis by ED severity was conducted. There was no evidence of degradation in erectile or ejaculatory function after PUL. SHIM and MSHQ-EjD scores were not different from control at 3 months but were modestly improved and statistically different from baseline at 1 year. Ejaculatory bother score was most improved with a 40 % improvement over baseline. Twelve-month SHIM was significantly improved from baseline for men entering the study with severe ED (p = 0.016). IPSS and Qmax were significantly superior to both control at 3 months and baseline at 1 year. There was no instance of de-novo sustained anejaculation or ED over the course of the study. The authors concluded that the PUL improved LUTS and urinary flow while preserving erectile and ejaculatory function.

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2014) states: "Current evidence on the efficacy and safety of insertion of prostatic urethral lift implants to treat lower urinary tract symptoms secondary to benign prostatic hyperplasia is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit."

Fernandes et al (2012) stated that prostatic artery embolization (PAE) gained special attention in the past years as a potential minimally invasive technique for BPH. Treatment decisions are based on morbidity and quality-of-life issues and the patient has a central role in decision-making. Medical therapy is a first-line treatment option and surgery is usually performed to

improve symptoms and decrease the progression of disease in patients who develop complications or who have inadequately controlled symptoms on medical treatment. The use of validated questionnaires to assess disease severity and sexual function, uroflowmetry studies, prostate-specific antigen and prostate volume measurements are essential when evaluating patients before PAE and to evaluate response to treatment. The authors stated that PAE may be performed safely with minimal morbidity and without associated mortality. The minimally invasive nature of the technique inducing a significant improvement in symptom severity associated with prostate volume reduction and a slight improvement in the sexual function are major advantages. However, as with other surgical therapies for BPH, up to 15 % of patients fail to show improvement significantly after PAE, and there is a modest improvement of the peak urinary flow.

Pisco et al (2011) evaluated whether prostatic arterial embolization (PAE) might be a feasible procedure to treat lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH). A total of 15 patients (age range of 62 to 82 years; mean age of 74.1 years) with symptomatic BPH after failure of medical treatment were selected for PAE with non-spherical 200-μm polyvinyl alcohol particles. The procedure was performed by a single femoral approach. Technical success was considered when selective prostatic arterial catheterization and embolization was achieved on at least one pelvic side. PAE was technically successful in 14 of the 15 patients (93.3 %). There was a mean follow-up of 7.9 months (range of 3 to 12 months). International Prostate Symptom Score decreased a mean of 6.5 points (p = 0.005), quality of life improved 1.14 points (p = 0.065), International Index of Erectile Function increased 1.7 points (p = 0.063), and peak urinary flow increased 3.85 mL/sec (p = 0.015). There was a mean prostate-specific antigen reduction of 2.27 ng/ml (p = 0.072) and a mean prostate volume decrease of 26.5 mL (p = 0.0001) by ultrasound and 28.9 mL (p = 0.008) by magnetic resonance imaging. There was 1 major complication (a 1.5-cm(2) ischemic area of the bladder wall) and four clinical

failures (28.6 %). The authors concluded that in this small group of patients, PAE was a feasible procedure, with preliminary results and short-term follow-up suggesting good symptom control without sexual dysfunction in suitable candidates, associated with a reduction in prostate volume.

Pisco et al (2013) evaluated the safety, morbidity, and short- and intermediate-term results of PAE for BPH after failure of medical treatment. Men older than 50 years with a diagnosis of BPH and moderate-to-severe lower urinary tract symptoms that were refractory to medical treatment for 6 months were eligible. PAE with non-spherical 80-180-µm (mean of 100-µm) and 180-300-µm (mean of 200-µm) polyvinyl alcohol particles was performed by means of a single femoral approach in most cases. Effectiveness variables of International Prostate Symptom Score (IPSS), quality of life (QOL) score, peak urinary flow, post-void residual volume, International Index Erectile Function (IIEF) score, prostate volume, and prostate-specific antigen level were assessed for up to 24 months after the procedure. Statistical analysis included the Kaplan-Meier method and random-effects generalized least squares regression with autoregressive disturbance. A total of 89 consecutive patients (mean age of 74.1 years) were included. PAE was technically successful in 86 of the 89 patients (97 %). Cumulative rates of clinical improvement in these patients were 78 % in the 54 patients evaluated at 6 months and 76 % in the 29 patients evaluated at 12 months. At 1-month follow-up, IPSS decreased by 10 points, QOL score decreased by 2 points, peak urinary flow increased by 38 %, prostate volume decreased by 20 %, post-void residual volume decreased by 30 ml, and IIEF score increased by 0.5 point (all differences were significant at $p < 0.01$). These changes were sustained throughout the observation period. There was one major complication: Intraluminal necrotic tissue attached to the bladder, which was removed with simple surgery and did not necessitate wall reconstruction. The authors concluded that PAE is a safe and effective procedure, with low morbidity, no sexual dysfunction, and good short- and intermediate-term symptomatic control associated with prostate volume reduction.

The 3 afore-mentioned studies appear to have been carried out by the same group of investigators. These short- and intermediate-term findings need to be validated by well-designed studies.

Grosso et al (2015) reported the clinical outcome after PAE in 13 consecutive patients with BPH and LUTS. From May 2012 to October 2013, these investigators performed PAE in 13 consecutive patients (mean age of 75.9 years) with BPH and LUTS and refractory to medical therapy; 7 patients had an indwelling bladder catheter. Clinical follow-up (mean follow-up time of 244 days) was performed using the IPSS, QOL, the IIEF, blood PSA testing and transrectal prostatic ultrasound (US) scan with volume and weight calculation at 3, 6 and 12 months. Pre-procedural CT angiography (CTA) was done for vascular mapping. Embolization was performed using Embosphere (300 to 500 micron). Technical success was defined when selective PAE was completed in at least 1 pelvic side. Clinical success was defined when symptoms and QOL were improved. Prostatic artery embolization was technically successful in 12/13 patients (92 %). In 1 patient, PAE was not performed because of tortuosity and atherosclerosis of iliac arteries. Prostatic artery embolization was completed bilaterally in 9/13 (75 %) patients and unilaterally in 3 (27 %). All patients removed the bladder catheter from 4 days to 4 weeks after PAE. They obtained a reduction in IPSS (mean of 17.1 points), an increase in IIEF (mean of 2.6 points), an improvement in QOL (mean of 2.6 points) and a volume reduction (mean of 28 %) at 12 months. The authors concluded that consistent with the literature, their experience showed the feasibility, safety and efficacy of PAE in the management of patients with LUTS related to BPH.   They stated that PAE may play an important role in patients in whom medical therapy has failed, and who are not candidates for surgery or TURP or refuse any surgical treatment. Moreover, they stated that larger case series and comparative studies with standard TURP can confirm the validity of the technique.

In a pilot study, Leoci et al (2014) studied the effectiveness of pulsed electromagnetic field therapy (PEMF) in dogs to modify

prostate blood flow and evaluated its effect on BPH. Pulsed electromagnetic field therapy (5 mins, twice-daily for 3 weeks) was performed on 20 dogs affected by BPH. Prostatic volume, Doppler assessment by ultrasonography, libido, semen quality, testosterone levels, and seminal plasma volume, composition and pH were evaluated before and after treatment. The 3 weeks of PEMF produced a significant reduction in prostatic volume (average 57 %) without any interference with semen quality, testosterone levels or libido. Doppler parameters showed a reduction of peripheral resistances and a progressive reduction throughout the trial of the systolic peak velocity, end-diastolic velocity, mean velocity, mean, and peak gradient of the blood flow in the dorsal branch of the prostatic artery. The pulsatility index and the resistance index did not vary significantly over time. The authors concluded that the effectiveness of PEMF on BPH in dogs, with no side effects, suggested the suitability of this treatment in humans and supported the hypothesis that impairment of blood supply to the lower urinary tract may be a causative factor in the development of BPH.

Russo et al (2014) stated that BPH is a very common condition in men over 50 years, often resulting in LUTS. Medical therapy aims at improving QOL and preventing complications. The range of drugs available to treat LUTS is rapidly expanding. Silodosin is a relatively new alpha 1-adrenoreceptor antagonist that is selective for alpha 1A-adrenergic receptor. While causing smooth muscle relaxation in the lower urinary tract, it minimizes blood pressure-related adverse effects. Tadalafil, a PDEs type 5 inhibitor, is a drug recently approved for the treatment of BPH/LUTS that challenges the standard therapy with alpha 1-blockers, especially in men with concomitant ED. Mirabegron is the first beta 3-adrenoceptor agonist approved for the treatment of symptoms of overactive bladder. Benign prostatic hyperplasia-related detrusor overactivity (DO) may be successfully targeted by mirabegron. Gonadotropin-releasing hormone antagonists, intra-prostatic injections with NX-1207 and vitamin D3 receptor analogs exerted beneficial effects on LUTS but need further evaluation in clinical studies. The

authors concluded that choosing the right treatment should be guided by patients' symptoms, co-morbidities and potential side effects of available drugs. Silodosin is a valid option for elderly and for people taking anti-hypertensive drugs.   They stated that BPH patients affected by ED can target both conditions with continuous tadalafil therapy. The encouraging data on mirabegron use in BPH-DO have to be further assessed in larger prospective RCTs.

Faber et al (2015) evaluated the safety and effectiveness of a novel robotic tissue ablation system (PROCEPT Aquablation™ System), in performing prostate ablation in a survival canine model. This novel technology uses a high-velocity saline stream that aims to selectively ablate prostatic glandular tissue while sparing collagenous structures such as blood vessels and capsule. Once the ablation is complete, a laser beam is captured by a low-pressure water jet to produce surface hemostasis. The extent and depth of ablation is pre-determined by endoscopic and transrectal ultrasonography guidance. The procedure was performed in 8 non-castrated male beagles aged 6 years or older (Acute 2, Chronic 6) through a previously created perineal urethrostomy. Aquablation time ranged from 40 to 84 seconds (mean of 60.5 sec). There was no active bleeding in any of the dogs during or after Aquablation. Water jet-guided laser coagulation was used for purposes of monitoring its safety and effectiveness; 5 of the 6 dogs reached the pre-determined 6-week mark. Complications included 2 dogs with infection successfully treated with antibiotics, a false passage created during catheter placement, and 2 bladder neck perforations (from mechanical insertion), 1 leading to euthanasia. Histologic evaluation at 6 weeks revealed a normal cellular architecture and full re-epithelialization of the treatment cavity. The authors reported the initial survival data in the animal model of a novel robotic device developed for managing symptomatic BPH. They stated that Aquablation produced ablation of adenomatous elements while preserving collagenous structures and is a promising technology for surgical management of symptomatic BPH.

Jones et al (2015) stated that PAE has emerged as a promising treatment for LUTS secondary to BPH. However, although it has gained increasing attention in radiology literature, it remains under-reported from a urologic perspective. These researchers provided an up-to-date review of this minimally invasive technique. Evidence suggests it is a promising and effective option for patients with large prostate volumes, multiple co-morbidities, and suboptimal results from pharmacotherapy. The authors concluded that larger, randomized studies with longer follow-up periods are needed for this technique to be formally established in the urology community.

Lebdai et al (2015) reviewed current knowledge on clinical outcomes and peri-operative complications of PAE in patients treated for LUTS related to BPO. A systematic review of the literature published from January 2008 to January 2015 was performed on PubMed/MEDLINE. A total of 57 articles were identified, and 4 were selected for inclusion in this review. Only 1 RCT compared TURP to PAE. At 3 months after the procedure, mean IPSS reduction from baseline ranged from 7.2 to 15.6 points. Mean urine peak-flow improvement ranged from +3.21 ml/s to +9.5 ml/s. When compared to TURP, PAE was associated with a significantly lower IPSS reduction 1 and 3 months after the procedure. A trend toward similar symptoms improvement was however reported without statistical significance from 6 to 24 months. Major complications were rare with 1 bladder partial necrosis due to non-selective embolization. Mild adverse events occurred in 10 % of the patients and included transient hyperthermia, hematuria, rectal bleeding, painful urination or acute urinary retention. Further comparative studies are mandatory to assess post-operative rates of complications, especially acute urinary retention, after PAE and standard procedures. The authors concluded that early reports suggested that PAE may be a promising procedure for the treatment of patients with LUTS due to BPO. However, the low level of evidence and short follow-up of published reports precluded any firm conclusion on its mid-term efficiency. They stated that further clinical trials are needed before it is used in clinical practice.

Bipolar Plasma Enucleation of the Prostate:

Geavlete et al (2013) evaluated the viability of bipolar plasma enucleation of the prostate (BPEP) by comparison with open transvesical prostatectomy (OP) in cases of large prostates with regard to surgical efficacy and peri-operative morbidity. These researchers compared the medium-term follow-up parameters specific for the 2 methods. A total of 140 BPH patients with prostate volume greater than 80 ml, Qmax less than 10 ml/s and IPSS greater than 19 were randomized in the 2 study arms. All cases were assessed pre-operatively and at 1, 3, 6 and 12 months after surgery by IPSS, Qmax , quality of life score (QoL) and PVR urinary volume. The prostate volume and PSA level were measured at 6 and 12 months. The BPEP and OP techniques emphasized similar mean operating durations (91.4 versus 87.5 mins) and resected tissue weights (108.3 versus 115.4 g). The post-operative hematuria rate (2.9 % versus 12.9 %) as well as the mean hemoglobin drop (1.7 versus 3.1 g/dL), catheterization period (1.5 versus 5.8 days) and hospital stay (2.1 versus 6.9 days) were significantly improved for BPEP. Re-catheterization for acute urinary retention was more frequent in the OP group (8.6 % versus 1.4 %), while the rates of early irritative symptoms were similar for BPEP and OP (11.4 % versus 7.1 %). During the follow-up period, no statistically significant difference was determined in terms of IPSS, Qmax , QoL, PVR, PSA level and post-operative prostate volume between the 2 series. The authors concluded that BPEP represents a promising endoscopic approach in large BPH cases, characterized by good surgical efficiency and similar BPH tissue removal capabilities compared with standard transvesical prostatectomy. They noted that BPEP patients benefited from significantly reduced complications, shorter convalescence and satisfactory follow-up symptom scores and voiding parameters.

da Silva et al (2015) stated that for decades, the monopolar TURP has been established as the minimally invasive surgical treatment for patients with BPH. In recent years, new technologies and devices emerged to reduce the morbidity and improve outcomes for this treatment approach. Bipolar energy

introduced the use of saline irrigation and laser technology increased the urological armamentarium to treat BPH. These researchers performed a systematic review of the literature regarding bipolar technology for the treatment of BPH; a Medline database search using the PRISMA methodology was carried out. Selected literature was restricted to articles published in English and published between 2005 and 2015. Articles regarding techniques using bipolar energy were included, while manuscripts that used a different technique, hybrid techniques, or techniques other than bipolar resection, bipolar vaporization, and bipolar enucleation were excluded. The use of bipolar energy in the endoscopic treatment of BPH presented a significant reduction in operative time, peri-operative complications, shorter catheterization time, reduced number of blood products transfused, and shorter hospital stay compared to standard techniques. Post-operative outcomes showed that bipolar energy was safe and offered significant outcome improvement when compared to traditional monopolar TURP. The authors concluded that the use of bipolar energy in the surgical treatment of patients with BPH is safe and is associated with improvements in peri-operative outcomes. They stated that short- and mid-term functional outcomes were comparable to standard techniques, but long-term functional outcomes need better clinical evaluation.

Histotripsy:

Histotripsy is a non-invasive, non-thermal, focused US therapy that mechanically liquefies targeted tissues within the body. It induces a process known as controlled cavitation (formation of microbubbles) within targeted tissues. The microbubbles oscillate back and forth, come together, and collapse in a very precise manner.

Nair and colleagues (2015) stated that LUTS are common and are often caused by BPH. Traditional surgical methods of open enucleation and TURP have been effective in alleviating these symptoms however, these are operator-dependent and often

come with significant side effects. These investigators discussed upcoming new surgical techniques in management of BPH. A systematic search of SCOPUS, MEDLINE, EMBASE and Cochrane databases was carried out using relevant key words. Intra-prostatic injections with a variety of agents have been explored as these can be readily performed under local anesthesia. Alcohol injections into the prostate have been abandoned due to potential side effects; but there has been ongoing development of 2 alternative agents, NX-1207 and PRX-302. Both have shown good safety profiles and early effectiveness in phase II studies. Thermal treatment with the Rezum device performed as an out-patient procedure has shown both safety and effectiveness in phase I and II studies. Aquablation showed promise in phase II studies with few side effects and is a relatively automated procedure, albeit requiring general anesthesia. Prostate artery embolization has been reported in a number of studies, but clinical outcomes have been unpredictable. Histotripsy has had a number of complications in animal models and despite technical improvement has not yet progressed beyond feasibility studies in humans. The authors concluded that some of the new techniques and technologies available for BPH have been shown to be relatively safe and effective and await validation with phase III clinical trials.

Aoun et al (2015) noted that BPH represents a spectrum of related LUTS. The cost of currently recommended medications and the discontinuation rate due to side effects are significant drawbacks limiting their long-term use in clinical practice. Interventional procedures, considered as the definitive treatment for BPH, carry a significant risk of treatment-related complications in frail patients. These issues have contributed to the emergence of new approaches as alternative options to standard therapies. These investigators reviewed the recent literature regarding the experimental treatments under investigation and presented the currently available experimental devices and techniques used under local anesthesia for the treatment of LUTS/BPH in the vast majority of cases. They discussed devices for delivery of thermal

treatment (microwaves, radiofrequency, high-intensity focused ultrasound, and the Rezum system), mechanical devices (prostatic stent and urethral lift), fractionation of prostatic tissue (histotripsy and aquablation), PAE, and intra-prostatic drugs; and analyzed evidence for the safety, tolerability, and efficacy of these "minimally invasive procedures".

Khokhlova et al (2015) stated that in high intensity focused ultrasound (HIFU) therapy, an ultrasound beam is focused within the body to locally affect the targeted site without damaging intervening tissues. The most common HIFU regime is thermal ablation. Recently there has been increasing interest in generating purely mechanical lesions in tissue (histotripsy). These investigators provided an overview of several studies on the development of histotripsy methods toward clinical applications. They presented 2 histotripsy approaches and examples of their applications. In one approach, sequences of high-amplitude, short (microsecond-long), focused ultrasound pulses periodically produce dense, energetic bubble clouds that mechanically disintegrate tissue. In an alternative approach, longer (millisecond-long) pulses with shock fronts generate boiling bubbles and the interaction of shock fronts with the resulting vapor cavity causes tissue disintegration. Recent pre-clinical studies on histotripsy were reviewed for treating BPH, liver and kidney tumors, kidney stone fragmentation, enhancing anti-tumor immune response, and tissue de-cellularization for regenerative medicine applications. Potential clinical advantages of the histotripsy methods were discussed. Histotripsy methods can be used to mechanically ablate a wide variety of tissues, while selectivity sparing structures such as large vessels. Both ultrasound and MRI can be used for targeting and monitoring the treatment in real time. The authors concluded that although the 2 approaches utilize different mechanisms for tissue disintegration, both have many of the same advantages and offer a promising alternative method of non-invasive surgery.

Phytotherapy:

Keehn and Lowe (2015) noted that the use of complementary and alternative medications has become a multi-million dollar business in the United States and comprises more than 50 % of all filled prescriptions for BPH in Europe. For the practicing urologist, understanding the phytotherapeutic agents available, their proposed mechanism of action, the research supporting their use; and their safety profiles has become increasingly important as more patients inquire into their use. A comprehensive literature search was conducted to identify pertinent articles pertaining to alternative and complementary treatment options for the management of BPH. Treatments demonstrating adequate clinical data, including Serona repens (saw palmetto), Pygeum africanum (African plum tree bark) , and Secale cereal (rye pollen), were selected for in depth review. Small clinical trials for each of the agents demonstrated mixed results while larger more soundly constructed studies found no significant benefit for the use of phytotherapy in the treatment of BPH. The authors concluded that based on the available literature, there is no evidence that phytotherapy significantly improves symptoms of BPH against placebo, despite being largely safe for ingestion. They stated that in patients with mild BPH symptoms who are reluctant to take standard pharmaceutical medications may try these agents provided that the patient understands their current limitations. Those with moderate or severe BPH should be discouraged from alternative and complementary treatments.

Furthermore, a Medscape review on "Benign prostatic hypertrophy" (Deters, 2015) states that "Phytotherapeutic agents and dietary supplements are considered emerging therapy by the AUA Guidelines panel and are not recommended for the treatment of BPH because of the lack of evidence at this time".   Examples of phytotherapeutic agents are African plum tree bark, pumpkin seeds, rye pollen, saw palmetto, South African star grass roots, and Stinging nettle roots.

The Rezum System:

TUNA using water vapor (ie, Rezūm System) delivers sterile water vapor (steam) transurethrally directly into hyperplastic tissue. Heat is released as the vapor condenses, causing cell death. The major difference between TUNA and Rezūm is how the RF energy is delivered to the prostate. In both cases energy is transferred via a transurethral needle injection. With the former, RF energy is directly delivered to the prostate tissue in a conductive manner. This causes necrosis of the tissue. However, in the Rezūm system the RF energy is used to heat sterile water to vapor and steam which when injected convectively treats the prostate tissue. This latter mechanism is intended to be safer for the patient and yield improved results.

Dixon et al (2015) evaluated the acute ablative characteristics of transurethral convective water vapor (steam) using the Rezum system in men with BPH through histologic and radiographic studies. A total of 7 patients were treated with transurethral intra-prostatic injections of sterile steam under endoscopic visualization followed by previously scheduled adenectomies. The extirpated adenomas were grossly examined followed by whole mount sectioning and staining with triphenyl-tetrazolium chloride (TTC) to evaluate thermal ablation. Histology was performed after hematoxylin and eosin staining on 1 prostate. After review of results from the first patient cohort, an additional 15 patients with clinical BPH were treated followed by gadolinium-enhanced magnetic resonance imaging (MRI) at 1 week. In the first patient cohort, gross examination of TTC-stained tissue showed thermal ablation in the transition zone. In addition, there was a distinct interface between viable and necrotic prostatic parenchyma. Histopathologic examination revealed TTC staining-outlined necrotic versus viable tissue. Gadolinium-enhanced MRIs in the cohort of 15 patients demonstrated lesion defects in all patients at 1 week post-procedure. Coalesced lesions were noted with a mean (± standard deviation) lesion volume of 9.6 ± 8.5 cm(3). The largest lesion volume was 35.1 cm(3). Ablation using vapor was rapid and remained confined to the transition zone, consistent with the thermodynamic principles of convective thermal energy transfer. The authors concluded that thermal ablation

was observed in all specimens. The resulting coalescing ablative lesions, as seen on MRI, were confined to the transition zone. They stated that these studies confirmed the ablative capabilities of vapor, validated the thermodynamic principles of convective heating, and allowed for further clinical studies.

McVary, et al. (2016) reported on the results of a multicenter, randomized, controlled study using transurethral prostate convective water vapor thermal energy to treat lower urinary tract symptoms associated with benign prostatic hyperplasia. Men 50 years old or older with an International Prostate Symptom Score of 13 or greater, maximum flow rate of 15 ml per second or less and prostate size 30 to 80 cc were randomized 2:1 between thermal therapy with the Rezūm® System and control. Thermal water vapor was injected into the transition zone and median lobe as needed. The control procedure was rigid cystoscopy with simulated active treatment sounds. The primary end point compared International Prostate Symptom Score reduction at 3 months. Treatment subjects were followed for 12 months. There were 197 men randomized (active 136, control 61). Thermal therapy and control International Prostate Symptom Score was reduced by 11.2 ± 7.6 and 4.3 ± 6.9 respectively (p <0.0001). Treatment subject baseline International Prostate Symptom Score of 22 decreased at 2 weeks (18.6, p=0.0006) and by 50% or greater at 3, 6 and 12 months, p <0.0001. The peak flow rate increased by 6.2 ml per second at 3 months and was sustained throughout 12 months (p <0.0001). No de novo erectile dysfunction was reported. Adverse events were mild to moderate and resolved quickly. The investigators concluded that convective water vapor thermal therapy provides rapid and durable improvements in benign prostatic hyperplasia symptoms and preserves erectile and ejaculatory function. Treatment can be delivered in an office or hospital setting using oral pain medication and is applicable to all prostate zones including the median lobe.

CPT Codes / HCPCS / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":	
CPT codes covered if selection criteria are met:	
52282	Cystourethroscopy, with insertion of permanent urethral stent
52450	Transurethral incision of prostate
52601	Transurethral electrosurgical resection of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included) [laser prostatectomy]
52647	Laser coagulation of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included if performed)
52648	Laser vaporization of prostate, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, internal urethrotomy and transurethral resection of prostate are included if performed) [TUVP]
52649	Laser enucleation of the prostate with morcellation, including control of postoperative bleeding, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, internal urethrotomy and transurethral resection of prostate are included if performed) [not covered for bipolar plasma enucleation]
53850	Transurethral destruction of the prostate tissue; by microwave thermotherapy [TUMT]
53852	by radiofrequency thermotherapy [TUNA]
Prostatic urethral lift:	

CPT codes covered if selection criteria are met:	
52441	Cystourethroscopy, with insertion of permanent adjustable transprostatic implant; single implant
52442	each additional permanent adjustable transprostatic implant (List separately in addition to code for primary procedure)
CPT codes not covered for indications listed in the CPB:	
Histotripsy, Phytotherapy (e.g., African plum tree bark, pumpkin seeds, rye pollen, saw palmetto, South African star grass roots, and Stinging nettle roots), Rezum system:	
No specific code	
0421T	Transurethral waterjet ablation of prostate, including control of post-operative bleeding, including ultrasound guidance, complete (vasectomy, meatotomy, cystourethroscopy, urethral calibration and/or dilation, and internal urethrotomy are included when performed)
37242	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; arterial, other than hemorrhage or tumor (eg, congenital or acquired arterial malformations, arteriovenous malformations, arteriovenous fistulas, aneurysms, pseudoaneurysms)
53855	Insertion of a temporary prostatic urethral stent, including urethral measurement
55873	Cryosurgical ablation of the prostate (includes ultrasonic guidance for interstitial cryosurgical probe placement)
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
Other CPT codes related to the CPB:	

52281	Cystourethroscopy, with calibration and/or dilation of urethral stricture or stenosis, with or without meatotomy, with or without injection procedure for cystography, male or female
53000 - 53010	Urethrotomy or urethrostomy, external (separate procedure)
53600 - 53621	Dilation of urethral stricture

HCPCS codes covered if selection criteria are met:

C9739	Cystourethroscopy, with insertion of transprostatic implant; 1 to 3 implants
C9740	4 or more implants

HCPCS codes not covered for indications listed in the CPB:

J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg
J9155	Injection, Degarelix, 1 mg
J9202	Goserelin acetate implant, per 3.6 mg
J9217	Leuprolide acetate (for depot suspension), 7.5 mg
J9218	Leuprolide acetate, per 1 mg
J9219	Leuprolide acetate implant, 65 mg
J9226	Histrelin implant (Supprelin LA), 50 mg
J3315	Injection, triptorelin pamoate, 3.75 mg
S0090	Sildenafil citrate, 25 mg

ICD-10 codes covered if selection criteria are met:

N35.010 - N35.9	Urethral stricture
N40.0 - N40.1	Enlarged prostate (EP)
N40.2 - N40.3	Nodular prostate

The above policy is based on the following references:

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Amendment to
Aetna Clinical Policy Bulletin Number: CPB 0079
Benign Prostatic Hypertrophy Treatments

There are no amendments for Medicaid